REMARKS

Claims 14, 16, 19, 20 and 21 have been amended to more fully define the present invention. No new matter has been added. Support for the amendments can be found on page 4, lines 5-6 and page 6, lines 6-14 of the Specification.

Rejections under 35 USC §112

The Examiner rejected claims 14-20 under 35 USC §112. Applicant has amended claim 14 to overcome the rejection.

Rejections under 35 USC §102/103

The Examiner rejected claims 14-18 (1) under 35 USC §102(b)/103(a) as anticipated by or obvious over Sanderson 4,541,944 and (2) under 35 USC §102(e)/103(a) as anticipated by or obvious over Del Duca et al 5,968,885 or 6,071,870. The Examiner rejected claim 19-21 (3) under 35 USC §103(a) as obvious over Sanderson 4,541,944 or Del Duca et al 5,968,885 or 6,071,870. The Examiner rejected claims 14-16 (4) under 35 USC §102(b)/103(a) as anticipated by or obvious over Scheuing et al 5,681,805 or 5,792,385 and (5) under 35 USC §102(e)/103(a) as anticipated by or obvious over Zhou et al 5,877,133 or Kott et al 6,117,357 or Miracle et al 6,096,098. The Examiner rejected claims 14-15 (6) under 35 USC §102(e)/103(a) as anticipated by or obvious over Scialla et al 6,099,587 or 5,997,585 or 5,900,187. The Examiner rejected claims 14 and 16-17 (7) under 35 USC §102(e)/103(a) as anticipated by or obvious over Choy7 6,010,994. The Examiner further rejected claims 17-21 (8) under 35 USC §103(a) as obvious over Scheuing et al 5,681,805 or 5,792,385, or Scialla et al 6,099,587 or 5,997,585 or 5,900,187, or Kott et al 6,117,357, or Miracle et al 6,096,098.

The Examiner stated, in part, that "Applicant's arguments for patentability ... [that the] claimed invention is directed towards a chemical and biological warfare decontamination solution [and that] the applied prior art solutions are directed to other intended uses, such as washing, bleaching, cleaning, and/or disinfecting". The Examiner concluded that this "argument of applicant, even if true, is irrelevant to the patentability of the pending claims". The Examiner based this conclusion on (1) the use of anticipation rejections and (2) that the courts have ruled numerous times that a novel intended use for an otherwise old or obvious composition does not render said composition patentably.

Applicant respectfully disagrees.

Unlike the present invention that is directed to chemical and biological decontamination, Sanderson '473 and '944, Del Duca et al '885 and '870, Scheuing et al '385 and '805, Zhou et al '137, Kott et al '357, Miracle et al '098, Scialla et al '587, '585, or '187, and Choy et al '994 all apparently relate to cleaning compositions (Sanderson '473 relates to "washing, bleaching, or disinfection" at col. 1, lns. 8-9; Sanderson '944 relates to "cleaning, bleaching or disinfection" at col. 1, lns. 10-11; and Del Duca et al '885 and '870 relate to "pretreater" at col. 1, ln. 6 and col. 1, ln. 9, respectively; Scheuing et al '385 and '805, Zhou et al '137 relate to "bleaching or cleaning applications" at col. 1, lns 62-63, col. 1, lns. 62-63 and col. 1, lns. 65-66, respectively, Kott et al '357 and Miracle et al '098 relate to "laundry, automatic dishwashing and hard surface cleaning compositions" at col. 1, lns. 17-19 and col. 1, lns. 14-16, respectively; Scialla et al '587 relates to a "pretreater" at col. 1, ln. 8, and Scialla et al '585 and '187 relate to "bleaching textiles" at col. 1, ln. 14 and col. 1, ln. 7, respectively; and Choy et al '994 refers to "bleaching and cleaning" at col.

1, lns. 16-17).

Applicant disagrees that Applicant's explicit limitation, both in the preamble and body of the claim, of a decontaminating solution and composition, merely sets forth the intended use of an old composition. The claim limitation of a decontaminating solution/composition in the instant claims differentiates the presently claimed invention from the cleaning compositions of the cited references. *In re Pearson*, 181 USPQ 641 (CCPA 1974) held that "[w]e do not mean to imply that terms which recite the intended use or a property of a composition can never be used to distinguish a new from an old composition. However, assuming their compliance with the definiteness requirement of the second paragraph of 35 U.S.C. 112, such terms must define, indirectly at least, some characteristic not found in the old composition" (*In re Pearson* at 644; see also *In re Tuominen*, 213 USPQ 89 (CCPA 1982) citing the *In re Pearson* case for a 102 rejection interpreting a preamble recitation of "sunscreen composition"). Unlike the *Tuominen* case, the present invention is limited by explicit limitations within the body of the instant claims, including "a decontaminating composition" that is further limited by the transition phrase "consisting essentially of". As such, the present invention defines solutions that are "nontoxic and useful in detoxifying/neutralizing a variety of chemical warfare agents" (*see* Specification at page 11, lines 20-21).

The references cited by the Examiner included formulations intended to be used in bleach formulations. Functionally, the cited patents and present invention using peracids in chemical warfare decontaminating solutions are quite different. In the bleach formulations, as taught by the cited references, the peracid is used to bleach a material (generally laundry) in contrast to the decontaminating solution formulation of the present invention utilizing the peracid to oxidize

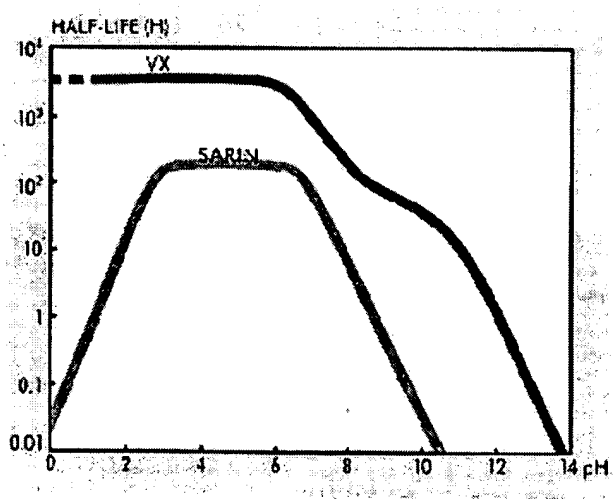
chemical agents. Bleach formulations do not work as chemical agent decontaminants. Bleaches decolorize by oxidizing, such bleachable soils as chromophoric systems with conjugated carbon double bonds in polymethine chains, or quinoidic systems that acquire the properties of a dye through the presence of amino, hydroxyl, or carboxylic groups. As a chemical warfare decontaminant formulation, the present invention uses aggressive oxidizers at fairly high concentrations for complete neutralization of the chemical agent. Oxidation of chemical agents, e.g., the sulfur atom in mustard gas/ nerve agent (VX) or the nitrogen atom in VX, necessitates large amounts of oxidizer, such as about 5% to 30% oxidizer.

Disinfecting compositions disclosed in the cited references also do not provide a basis, either as a 102 or 103 rejection, for the presently claimed invention. Decontamination is the ridding of contamination whereas disinfection frees from infection esp. by destroying harmful microorganisms (*see* Webster's Ninth New Collegiate Dictionary, Merriam-Webster Inc. 1987). As the disclosures of the cited references teach disinfection, or other types of harsh cleaning, these references disclose compositions unsuitable for decontamination of "equipment, personnel, or the like" (Specification at page 12, lines 4-5) and/or are functionally inept as decontaminating compositions. Applicant notes that the examples of the cited patents generally teach away from the present invention. For example in Example IX of United States Patent no. 6,096,098 to Miracle et al, formulations of 7.0% and 5.0% Bleach Activator A with 10.0% Hydrogen Peroxide are listed. However, the pH 4 of the example makes this inappropriate for use in decontamination formulations. As well known in the art of chemical warfare decontamination, G agents are susceptible to base, *i.e.*, high pH, hydrolysis, which is contrary to the teachings of the references. Likewise VX, for example, does not readily

decompose at an acidic pH, such as the pH of 4 in Example IX. Applicant has attached a copy of an article "Nerve Agents", at www. Chefnoah.com /germ% 20warfare /nerve_agents.htm (copyright 2002 Chef Noah), which states (at page 4):

> "The most important chemical reactions of nerve agents take place directly at the phosphorus atom. The P-X bond is easily broken by nucleophilic reagents, such as water or hydroxyl ions (alkali). In aqueous solution at neutral pH the nerve agents decompose slowly, whereas the reaction is greatly accelerated following the addition of alkali. The result is a non-toxic phosphoric acid.
>
> The pH-dependence on the rate of hydrolysis for sarin and VX at 25 °C expressed as half-life (hours). The curves have been calculated from laboratory experiments where pH was kept constant. On moist ground or snow, hydrolysis may be faster than shown in the figure as a result of auto-catalysis. The acidic hydrolysis products formed namely lead to a gradually lower pH and thus faster degradation."

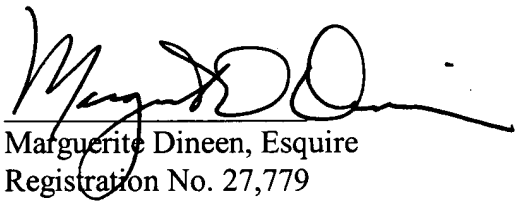
Additionally, the article provided the graph:



Applicant submits that the presently presented claims "define, indirectly at least, some characteristic not found in the old composition" of the cited prior art. Applicant further submits that the present invention, as claimed, is novel and not obvious over the cited references.

Accordingly, Applicant requests reconsideration and allowance of claims 14-16 and 19-21, as amended herein. The Examiner is invited to contact the attorney of record, listed below, with any questions or other matters to advance the present application.

Respectfully submitted,



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Nerve Agents

Lethal organo-phosphorus compounds inhibiting cholinesterase

Nerve Agents

Source: A FOA Briefing Book on Chemical Weapons

Among lethal CW agents, the nerve agents have had an entirely dominant role since the Second World War. Nerve agents acquired their name because they affect the transmission of nerve impulses in the nervous system. All nerve agents belong chemically to the group of organo-phosphorus compounds. They are stable and easily dispersed, highly toxic and have rapid effects both when absorbed through the skin and via respiration. Nerve agents can be manufactured by means of fairly simple chemical techniques. The raw materials are inexpensive and generally readily available.

It was not until the early 1930's that German chemists observed that organo-phosphorus compounds could be poisonous. In 1934, Dr Gerhard Schrader, a chemist at IG Farben, was given the task of developing a pesticide. Two years later a phosphorus compound with extremely high toxicity was produced for the first time. According to contemporary regulations, discoveries with military implications had to be reported to the military authorities, which was also done with Schrader's discovery. This phosphorus compound, given the name tabun, was the first of the substances later referred to as nerve agents.

A factory for production of the new CW agent was built and a total of 12 000 tons of tabun were produced during the years 1942-1945. At the end of the war the Allies seized large quantities of this nerve agent. Up to the end of the war, Schrader and his co-workers synthesized about 2 000 new organo-phosphorus compounds, including sarin (1938). The third of the "classic" nerve agents, soman, was first produced in 1944. These three nerve agents are known as G agents in the American nomenclature. The manufacture of sarin never started properly and up to 1945 only about 0.5 ton of this nerve agent was produced in a pilot plant.

Immediately after the war, research was mainly concentrated on studies of the mechanisms of the nerve agents in order to discover more effective forms of protection against these new CW agents. The results of these efforts led, however, not only to better forms of protection but also to new types of agents closely related to the earlier

ones.

By the mid-1950's a group of more stable nerve agents had been developed, known as the V-agents in the American nomenclature. They are approximately ten-fold more poisonous than saran and are thus among the most toxic substances ever synthesized.

The first publication of these substances appeared in 1955. The authors, R. Ghosh and J.F. Newman, described one of the substances, known as Amiton, as being particularly effective against mites. At this time, intensive research was being devoted to the organo-phosphorus insecticides both in Europe and in the United States. At least three chemical firms appear to have independently discovered the remarkable toxicity of these phosphorus compounds during the years 1952-53. Surprisingly enough, some of these substances were available on the market as pesticides. Nonetheless, they were soon withdrawn owing to their considerable toxicity also to mammals.

In the United States, the choice fell in 1958 on a substance known by its code name VX as suitable as a CW agent of persistent type. Full-scale production of VX started in April 1961 but its structure was not published until 1972.

Physical and Chemical Properties

The most important nerve agents included in modern CW arsenals are:

- Tabun, O-ethyl dimethylamidophosphorylcyanide, with the American denomination GA. This nerve agent is the easiest to manufacture. Consequently, it is more likely that developing countries start their CW arsenal with this nerve agent whereas industrialized countries consider tabun to be out-of-date and of limited use.
- Sarin, isopropyl methylphosphonofluoridate, with the American denomination GB, a volatile substance mainly taken up through inhalation.
- Soman, pinacolyl methylphosphonofluoridate, with the American denomination GD, a moderately volatile substance which can be taken up by inhalation or skin contact.
- Cyclohexyl methylphosphonofluoridate, with the American denomination GF, a substance with low volatility which is taken up through skin contact and inhalation of the substance either as a gas or aerosol.
- O-ethyl S-diisopropylaminomethyl methylphosphonothiolate, better known under the American denomination VX, a persistent

substance which can remain on material, equipment and terrain for long periods. Uptake is mainly through the skin but also through inhalation of the substance as a gas or aerosol.

The formulae for some nerve agents are:

- Tabun, GA: $(CH_3)_2N\text{-}P(=O)(\text{-}CN)(\text{-}OC_2H_5)$
- Sarin, GB: $CH_3\text{-}P(=O)(\text{-}F)(\text{-}OCH(CH_33)_2)$
- Soman, GD: $CH_3\text{-}P(=O)(\text{-}F)(\text{-}CH(CH_3)C(CH_3)_3$
- GF: $CH_3\text{-}P(=O)(\text{-}F)(\text{cyklo-}C_6H_{11})$
- VX: $CH_3\text{-}P(=O)(\text{-}SCH_2CH_2N[CH(CH_3)_2]_2)(\text{-}OC_2H_5)$

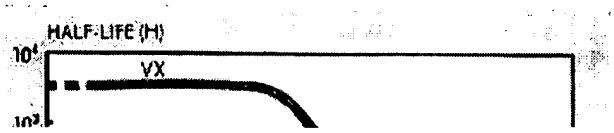
The same type of phosphorus compounds are used as, for example, insecticides. In the structure of insekticides P(=O) has generally been replaced by P(=S) and a less reactive group than (-F), (-CN) or ($\text{-}SCH_2CH_2N[CH(CH_3)_2]_2$) is used.

All nerve agents in pure state are colorless liquids. Their volatility varies widely. The consistency of VX may be likened to an involatile oil and is therefore classified as belonging to the group of persistent CW agents. Its effect is mainly through direct contact with the skin. Sarin is at the opposite extreme, being an easily volatile liquid (comparable with, e.g., water), and mainly taken up through the respiratory organs. The volatilities of soman, tabun and GF are between those of sarin and VX.

By addition of a thickener it is possible for, e.g., soman, to be transferred from the category of volatile CW agents to the persistent agents.

Sarin is very soluble in water whereas other nerve agents are more sparingly soluble. VX has the unexpected property of being soluble in cold water but sparingly soluble in warm water (>9.5 °C).

The most important chemical reactions of nerve agents take place directly at the phosphorus atom. The P-X bond is easily broken by nucleophilic reagents, such as water or hydroxyl ions (alkali). In aqueous solution at neutral pH the nerve agents decompose slowly, whereas the reaction is greatly accelerated following the addition of alkali. The result is a non-toxic phosphoric acid.



The pH-dependence on the rate of hydrolysis for sarin and

VX at 25 °C expressed as half-life (hours). The curves have been calculated from laboratory experiments where pH was kept constant. On moist ground or snow, hydrolysis may be faster than shown in the figure as a result of auto-catalysis. The acidic hydrolysis products formed namely lead to a gradually lower pH and thus faster degradation.

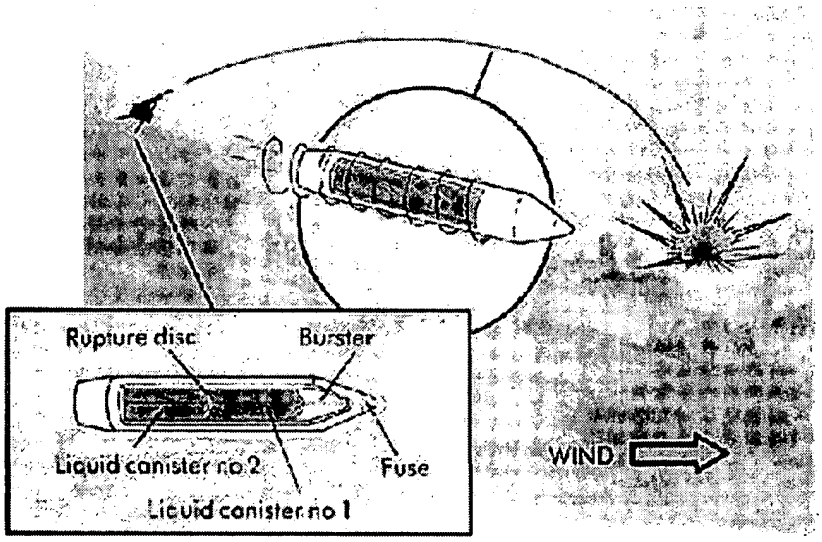
The formation of the non-toxic phosphoric acid is also accelerated by rise in temperature or by a catalyst (e.g., hypochlorite ions from bleaching powder). This hydrolysis forms the basis of most decontamination procedures utilizing decomposition. In general, we may assume that an area exposed to G-agents decontaminates itself within a few days. However, V-agents may remain on the ground for several weeks because of their greater stability with respect to water and their much lower volatility. At pH-levels between 7 and 10 large quantities of VX are transformed into an extremely non-volatile product of hydrolysis which is incapable of penetrating skin. Admittedly, this is less toxic than VX but still implies a risk during decontamination.

The nucleophilic attack on the phosphorous atom (P) also forms the basis of different types of coulour reaction used in detecting nerve agents.

Binary Technology

Most chemical ammunition can be described as unitary, which implies that it contains one active ready-to-use CW agent. Binary technology implies that the final stage in the synthesis of the nerve agent is moved from the factory into the warhead, which thus functions as a chemical reactor. Two initial substances which are stored in separate containers are mixed and allowed to react and form the nerve agent when the ammunition (bomb, projectile, grenade, etc.) is on its way towards the target.

Until the actual moment of use, the ammunition contains only relatively non-toxic initial substances. It is therefore considered to be safer to manufacture, store, transport and, finally, destroy. However, some critics question whether this practically untested type of new ammunition is reliable. The technique for mixing substances in bombs and rockets is complicated and requires space. The reaction has to be controlled (e.g., the temperature) and the process should preferably take place without solvents.



The principle for the use of binary weapons. *Two canisters with the two liquid components are placed one after the other in the shell. When the shell is fired, forces of inertia will press the liquid contents in the front canister backwards and burst the wall separating the canisters. The rifling in the barrel gives the shell a spinning velocity of about 15,000 r.p.m. which contributes to the mixing.*

In 1991 Iraq declared to the United Nations Special Commission (UNSCOM) a different binary munitions concept. According to this the munitions were stored containing one component. Shortly before use the munitions were opened and the second component was added. Thus the reaction began even before the munitions were launched.

Binary components for the three most common nerve agents (American code names are given in brackets) are the following:

- Sarin (GB-2): methylphosphoryldifluoride (DF) + isopropanol. The isopropanol is included in a mixture (OPA) with isopropylamine which binds the hydrogen fluoride generated.
- Soman (GD-2): methylphosphoryldifluorid (DF) + pinacolylalcohol.
- VX-2: O-ethyl O-2-diisopropylaminoethyl methylphosphonite (QL) + sulphur.

Mechanism of Action

A characteristic of nerve agents is that they are extremely toxic and that they have very rapid effect. The nerve agent, either as a gas, aerosol or liquid, enters the body through inhalation or through the skin. Poisoning may also occur through consumption of liquids or foods contaminated with nerve agents.

The route for entering the body is of importance for the period required for the nerve agent to start having effect. It also influences the symptoms developed and, to some extent, the sequence of the different symptoms. Generally, the poisoning works faster when the agent is absorbed through the respiratory system than via other routes. This is because the lungs contain numerous blood vessels and the inhaled nerve agent can therefore rapidly diffuse into the blood circulation and thus reach the target organs. Among these organs, the respiratory system is one of the most important. If a person is exposed to a high concentration of nerve agent, e.g., 200 mg sarin/m^3 (see table) death may occur within a couple of minutes.

Poisoning takes longer when the nerve agent enters the body through the skin. Nerve agents are more or less fat-soluble and can penetrate the outer layers of the skin. However, it takes some time before the poison reaches the deeper blood vessels. Consequently, the first symptoms do not occur until 20-30 minutes after the initial exposure but subsequently the poisoning process may be rapid if the total dose of nerve agent is high. The toxic effect of nerve agents depends on them becoming bound to an enzyme, acetylcholinesterase, and thereby inhibit this vital enzyme's normal biological activity in the cholinergic nervous system.

Symptoms

When exposed to a low dose of nerve agent, causing minor poisoning, characteristic symptoms are increased production of saliva, a running nose and a feeling of pressure on the chest. The pupil of the eye becomes contracted (miosis) which impairs night-vision. The accommodation capacity of the eye is also reduced so that short-range vision deteriorates and the victim feels pain when he tries to focus on an object nearby. This is accompanied by headache. More unspecific symptoms are tiredness, slurred speech, hallucinations and nausea.

Exposure to a higher dose leads to a more dramatic development and symptoms are more pronounced. Bronchoconstriction and secretion of mucous in the respiratory system leads to difficulty in breathing and

to coughing. Discomfort in the gastrointestinal tract may develop into cramp and vomiting. Involuntary discharge of urine and defecation may also form part of the picture. The discharge of saliva is powerful and the victim may experience running eyes and swetting. Symptoms from the skeletal muscles are very typical. If the poisoning is moderate, this may express itself as muscular weakness, local tremors or convulsions.

When exposed to a high dose of nerve agent, the muscular symptoms are more pronounced. The victim may suffer convulsions and lose consciousness. To some extent, the poisoning process may be so rapid that earlier mentioned symptoms may never have time to develop.

Muscular paralysis caused by nerve agents also affects the respiratory muscles. Nerve agents also affect the respiratory center of the central nervous system. The combination of these two effects is the direct cause of death. Consequently, death caused by nerve agents is a kind of death by suffocation.

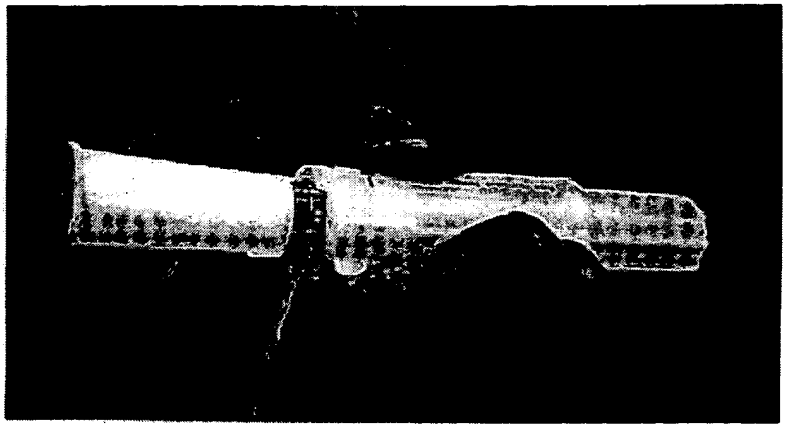
The figure shows examples of poisoning results caused by different doses of sarin vapor. In similarity to other poisons, different individuals are more or less sensitive to nerve agents. The figure shows that the lethal dose for the most sensitive individuals is about 70 $mg \cdot min/m^3$ and about twice this level for more resistant people.

The toxic effect depends on both the concentration of nerve agent in the air inhaled (C) and the time of exposure (t). In extremely high concentrations there is a simple relationship, C t, which gives a certain toxic effect. Inhalation of sarin vapor with a concentration of 100 mg/m^3 for one minute gives the same result as inhalation of 50 mg/m^3 for two minutes. However, at low concentrations this relationship does not apply since the human body is capable of some degree of detoxification. In order to obtain a corresponding effect, it is then necessary to have relatively longer periods of exposure. The values given in the table for toxicity of nerve agents apply to high concentrations.

Antidotes and Methods of Treatment

Nerve agents have an extremely rapid effect. If medical methods of treatment are to serve any purpose, they must be introduced immediately. In many countries, the armed forces have access to an auto-injector containing antidotes to nerve agents. It is so simple to use that the soldier can easily give himself or another person an

intramuscular injection.



The Swedish auto-injector.

One example is the Swedish auto-injector, which contains two active components: HI-6 (500 mg) and atropine (2 mg). HI-6 is an oxime which directly reacts with the cause of the injury, i.e., nerve agent-inhibited acetylcholinesterase. HI-6 functions as a reactivator which restores the enzyme to an operational condition. Oximes have a poor penetration capacity into the brain and thus mainly work in the peripheral nervous system.

The various nerve agents cause poisoning which are more or less easy to treat with oximes. From this standpoint, VX and sarin are the easiest to treat and all oximes used increase the chances of surviving poisoning with these nerve agents. Obidoxime is the most effective against tabun poisoning but also HI-6 has a positive effect. Soman causes the most difficultly treated poisoning and can only be treated with HI-6.

Soman poisoning is complicated by the inhibited enzyme going through an "ageing" process. Following the ageing the enzyme cannot be reactivated by any oxime. It is possible that HI-6 has some further positive antidote effect in addition to its reactivating ability.

The other active component in the auto-injector is atropine. Atropine is the classical antidote in cases of poisoning by organo-phosphorus compounds. It is a medication which relieves the symptoms but does not attack the cause of the injury. Atropine becomes bound to the receptors for acetylcholine, which are present in the cholinergic synapse (see figure). When acetylcholine is bound, the signal is transmitted but if atropine has become bound to the receptor, then no such transmission takes place. Atropine thus gives protection against the excess of acetylcholine which results from inhibition of acetylcholinesterase. Atropine has effects only within certain parts of the cholinergic nervous system.

There are two types of acetylcholine receptors, the nicotinic which are

found, e.g., in the skeletal muscles, and the muscarinic, which are found in, e.g., smooth muscles, glands and the central nervous system. Atropine blocks the muscarinic receptors. Atropine and oxime may therefore be considered to complement each other and the two antidotes also have a synergetic effect, i.e., they boost each other.

An additional auto-injector can be given to victims of nerve agents if their situation does not improve within ten minutes. Subsequently, the victim should be treated by qualified medical staff who should initially inject additional atropine and an anti-convulsant drug, diazepam. In cases of severe poisoning by nerve agents, large doses of atropine (grammes) may be required. The level of operational acetylcholinesterase is gradually restored by the body's own production but this process requires at least two weeks. During this period, and possibly also later, the victim may require medical care not only for mental disorders such as difficulty in sleeping, amnesia, difficulties in concentrating, and anxiety, but also for muscular weakness. Mental problems may also occur after long exposure to extremely low concentrations to nerve agents.

There are also medical antidotes which can be taken preventively. These antidotes are taken as tablets and used when ordered in connection with maximum C-preparedness. One of the tablets contains a carbonate, pyridostigmine, as active ingredient. Pyridostigmine inhibits acetylcholinesterase and protects the enzyme against inhibitory effects of nerve agents. The dose is low and leads to about 25 per cent inhibition. The pyridostigmine-inhibited enzyme is continuously released to active state and thereby can reasonably effectively maintain the transfer of nerve impulses despite injury caused by nerve agents. The effect is restricted to the peripheral cholinergic nervous system since the substance does not enter the brain.

Pyridostigmine does not cause any side effects since there is a large excess of enzyme in the cholinergic synapse. In actual fact, 1-2 per cent of functional enzyme is sufficient to have a functioning synapse. This explains why carbamate pretreatment has such good effect.

Pretreatment with carbonate should be combined with oxime therapy (the auto-injector) after the poisoning in order to provide maximum effect. This combination reduces the toxic effects of all nerve agents.

A diazepam tablet is also generally given as a pretreatment, primarily affecting the central nervous system. Diazepam strengthens the effect of other nerve agent antidotes. There will be better prospects of survival and less injury. Diazepam also provides protection against

permanent brain damage which may result from heavy exposure to nerve agents.

Pretreatment has best effect if a warning system is available and operative, since the tablets need about 30 min. to have effect after being swallowed. The best protective effect is achieved after about two hours, which is followed by decreasing efficacy. If the situation so requires, treatment can be repeated at eight-hourly intervals for some days. The tablets should not be taken once nerve agent injury has occurred. Admittedly, diazepam has a positive effect but pyridostigmine at that stage will aggravate the injury.

Toxicity of the most important nerve agents to man

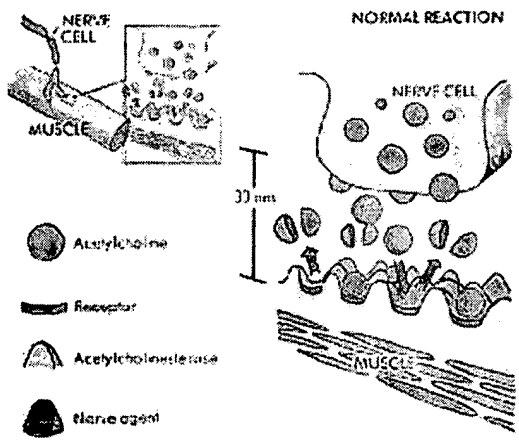
	LCt_{50}	LD_{50}
	Inhalation	Skin
	$mg \cdot min/m^3$	mg/individual
Tabun	200	4 000
Sarin	100	1 700
Soman	100	300
VX	50	10

The values are estimates of the doses which have lethal effects on man. LD_{50} expresses the dose at which 50 per cent of the exposed population will die as a result of their injuries. A different measure is used for inhalation, the product of the concentration (C) and the length of exposure (t). Again, L stands for lethal and 50 for 50 per cent effect. The toxicity sequence is the same for the two routes of exposure but the differences are much greater in skin exposure. This is mainly caused by the more volatile nerve agents evaporating from naked skin. If the evaporation is prevented, e.g., by tightly fitting clothing, the difference will be less.

Physical Properties of Nerve Agents

Property	Tabun	Sarin	Soman	GF	VX
Molecular weight	162.1	140.1	182.2	180.2	267.4
Density g/cm^3 *	1.073	1.089	1.022	1.120	1.008
Boiling-point °C	247	147	167	92**	300
Melting-point °C	-50	-56	-42	< -30	-39
Vapour pres. mm Hg *	0.07	2.9	0.3	0.06	0.0007
Volatility mg/m^3 *	600	17,000	3,900	600	10
Solubility in water % *	10	oo	2	~2	3 (oo < 9,5 °C)

* = at 25 °C ** = at 10 mm Hg



A simplified picture of a cholinergic synapse, with the nerve in which acetyllcholine is formed and the receiving side (muscles, glands, etc.) with receptors. Acetylcholine is formed and released from the nerve cell. On the other side of the synapse it binds to a muscle cell receptor for a split second. The signal to, e.g. bend an arm or take a breath has now been transferred from the nervous system to the performing muscle. In the presence of nerve agent the enzyme acetylcholinesterase, which is responsible for breaking down acetylcholine, is inhibited. The receptor keep on sending signals to the muscle cell, which leads to muscle cramp.

Effect of Nerve Agents and Antidotes on the Enzyme Acetylcholinesterase

The toxic effect of nerve agents depends on the substance inhibiting the enzyme acetylcholinesterase in the cholinergic nerve system. This enzyme is responsible for breaking down the signal substance acetylcholine, a process requiring two steps - acetylation by means of a serine in the active site and hydrolysis:

Enzyme-OH + $CH_3C(=O)-O-(CH_2)_2-N^+(CH_3)_3$
reacts with the release of chorine to give
Enzyme-O-$C(=O)-CH_3$
which is rapidly hydrolyzed to
Enzyme-OH + CH_3COOH

Degradation of the signal substance in the cholinergic synapse takes place extremely rapidly depending on the enzyme being available in large amounts and also since it is extremely effective. Under optimum conditions, each enzyme molecule hydrolyzes about 15 000 acetylcholine molecules per second. The reaction mechanism for nerve agents is similar but with the important difference that the rate of the final, hydrolyzing step is negligible. Consequently, the enzyme becomes irreversibly inhibited, with the nerve agent covalently bound to the enzyme via the serine in the active site.

Enzyme-OH---X-$P(=O)(R_1)(-OR_2)$
releases X^- to give
Enzyme-O-$P(=O)(R_1)(-OR_2)$

Inhibition of acetylcholinesterase is thus a progressive process and the degree of inhibition depends not only on the concentration of nerve agent but also on the time of exposure. Soman is the most potent inhibitor of acetylcholinesterase among the nerve agents. A concentration of 10^{-9} M is sufficient to inhibit the enzyme by more than 50 per cent within 10 minutes.

Reactivation Using Oxime

Oximes, with the general formula R-CH=NOH, can reactivate the phosphorylated enzyme. The oxime attacks the P-O bond whereby an operational enzyme and a phosphorylated oxime, which is rapidly hydrolyzed to non-toxic products, are formed. The efficiency of such reactivation depends strongly on the types of all the three components involved - enzyme, oxime and nerve agent.

"Ageing"

In the "ageing" reaction, the phosphorylated enzyme is dealkylated:

Enzyme-O-P(=O)(R_1)(-OR_2)
reacts to give
Enzyme-O-P(=O)(R_1)-OH

The reaction is catalyzed by the enzyme itself and the reaction may be extremely fast. Soman-inhibited acetylcholinesterase becomes "aged" within a few minutes. After the "ageing", the inhibited enzyme is even more resistant to hydrolysis and reactivation with oxime is without effect.

Pretreatment With the Carbonate Pyridostigmine

Carbonates, with the general formula R_1R_2-N-C(O)-O-R_3, inhibit acetylcholinesterase. They carbamylate the enzyme with a mechanism analogous to the substrate and nerve agent reactions. The carbamylated enzyme hydrolyzes slowly with a half-life of about 30 minutes.

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